PATENT ABSTRACTS OF JAPAN

(11)Publication number : 09-263579
(43)Date of publication of application : 07.10.1997

(51)Int.CI.

C07D211/46
A61K 9/107
A61K 9/127
A61K 9/14
A61K 9/16
A61K 9/50
A61K 31/70
A61K 31/71
A61K 31/715
A61K 38/00
A61K 38/43
A61K 38/55
A61K 51/00
A61K 45/00
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A61K 45/00
A61K 45/00
A61K 47/22
A61K 49/00
A61K 49/04
C07D211/34
C07D211/54
C07D211/62
//(A61K 47/22
A61K 47:24)

(21)Application number : 08-076260
(22)Date of filing : 29.03.1996

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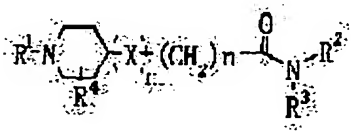
(54) PIPERIDINE DERIVATIVE AND DRUG CARRIER CONTAINING THE DERIVATIVE AS CONSTITUENT COMPONENT

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject new compound derivative consisting of a specific piperidine derivative having amide group and useful e.g. as a constituent component of a drug carrier composed of e.g. a closed acinus capable of efficiently and safely introducing a genetic substance and drug into a cell or a diseased part.
SOLUTION: This new piperidine derivative is expressed by formula I [R1 is H or a 1-8C alkyl or alkenyl; R2 and R3 are each H (R2 and R3 are not simultaneously H) or a 1-25C alkyl or alkenyl; R4 is H or a 1-8C alkyl or alkenyl; X is O or S; (m) is 0 or 1; (n) is 0 or 1-10]. It is useful e.g. as a constituent component of a drug carrier composed of a closed acinus, etc., and capable of efficiently and safely introducing a genetic substance and drug into a cell or a diseased part. The compound can be produced by reacting a piperidine- carboxylic acid derivative of formula II with an amine derivative of formula III.



I

II

III

LEGAL STATUS

[Date of request for examination] 04.03.2003

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

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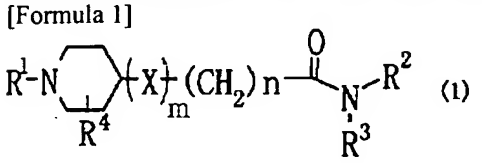
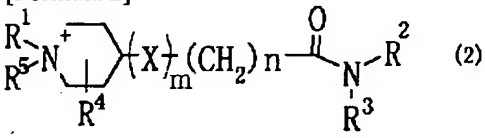
CLAIMS

[Claim(s)]
[Claim 1] The piperidine derivative shown by the following general formula 1.
[Formula 1]



(1)

R1 is the alkyl group or alkenyl machine of hydrogen and carbon numbers 1-8 among a formula 1. R2 and R3 Or it differs and is the alkyl group or alkenyl machine of hydrogen (however, when both R2 and R3 are hydrogen, it removes), and carbon numbers 1-25. the same -- R4 Hydrogen, the alkyl group of carbon numbers 1-8 or an alkenyl machine, and X are -O- or -S-, m is 0 or 1 and n shows the integer of 0, or 1-10. Moreover, when an asymmetrical carbon exists in a molecule, any of racemic modification and the optically active substance are sufficient as the compound.
[Claim 2] The piperidine derivative shown by the following general formula 2.
[Formula 2]



(2)

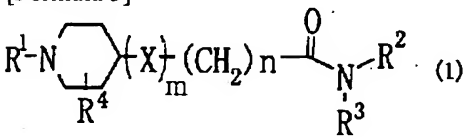
Or it differs and is the alkyl group or ARUKENIRU machine of carbon numbers 1-8. the inside of a formula 2, and R1 and R5 are the same -- R2 and R3 Or it differs and is the alkyl group or ARUKENIRU machine of hydrogen (however, when both R2 and R3 are hydrogen, it removes), and carbon numbers 1-25. the same -- R4 Hydrogen, the alkyl group of carbon numbers 1-8 or an ARUKENIRU machine, and X are -O- or -S-, m is 0 or 1 and n shows the integer of 0, or 1-10. Moreover, when an asymmetrical carbon exists in a molecule, any of racemic modification and the optically active substance are sufficient as the compound.
[Claim 3] Medicine support which makes a constituent a piperidine derivative according to claim 1 to 2.
[Claim 4] Medicine support according to claim 3 which comes to enclose the medicine for diagnosing and/or treating with the aforementioned medicine support.
[Claim 5] Medicine support according to claim 3 to 4 which consists of a minute particle whose path of the aforementioned support is 0.02-250 micrometers.
[Claim 6] Medicine support according to claim 3 to 5 by which the aforementioned support is constituted from at least one of a macromolecule, fine aggregate, particle, minute sphere, and nano corpuscle, a liposome, and emulsions.
[Claim 7] Medicine support according to claim 3 to 6 in which the aforementioned support contains a lipid other than phospholipid or its derivative, and/or phospholipid or its derivative, a stabilizing agent, an antioxidant, and/or other surface ornamentation agents.
[Claim 8] Medicine support according to claim 3 to 7 whose medicines for above-diagnosing and/or treating are a nucleic acid, a polynucleotide, a gene, and its analog.
[Claim 9] The medicine for above-diagnosing and/or treating An anti-inflammatory agent, an anticancer agent, An enzyme agent, an enzyme inhibitor, an antibiotic, an anti-oxidant, a lipid incorporation inhibitor, a hormone drug, An angiotensin conversion enzyme inhibitor, an angiotensin acceptor antagonist, Proliferation and the migration inhibitor of a smooth muscle fiber, a platelet aggregation inhibitor, the isolation inhibitor of a chemical mediator, Medicine support according to claim 3 to 7 which is proliferation or the inhibitor, the aldose reductase inhibitor, the mesangial-cell growth inhibition agent, the lipoxygenase inhibitor, the immunosuppresant, the immunostimulator, antivirotic, or radical SUKABEN char of an endothelial cell.
[Claim 10] Medicine support according to claim 3 to 7 whose medicines for above-diagnosing and/or treating are a glycosaminoglycan and its derivative.
[Claim 11] Medicine support according to claim 3 to 7 whose medicines for above-diagnosing and/or treating are oligo and/or polysaccharides, and those derivatives.

[Claim 12] Medicine support according to claim 3 to 7 whose medicine for above-diagnosing and/or treating is protein or a peptide.
[Claim 13] Medicine support according to claim 3 to 7 whose medicines for above-diagnosing and/or treating are various in-the-living-body diagnostic drugs, such as X contrast medium, radioisotope indicator nuclear-medicine-diagnosis medicine, and a diagnostic drug for a nuclear-magnetic-resonance diagnosis.

[Translation done.]

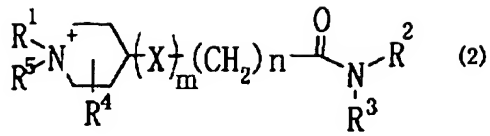
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the medicine support which makes a constituent a new piperidine derivative and new it.
[0002]
[Description of the Prior Art] In recent years, research which it is going to apply to a drug delivery system (DDS is called hereafter) by making synizesis parcels, such as a liposome, an emulsion, and a lipid microsphere, into medicine support is done briskly. These synizesis parcel was not able to conquer difficulty in various fields when it is prepared as a basic film constituent, however phospholipid, its derivative or a sterol, lipids other than phospholipid, etc. are generally applied to practice, such as a fall of the retentivity in condensation of synizesis parcels, and the inside of the body, only by these basic constituent. Furthermore, it was very difficult to have made a medicine actually reach the target part as a DDS tablet.
[0003] Then, the attempt which cation-izes the front face of a synizesis parcel object in the physiological pH range is also performed by carrying out little combination of the cation-ized lipids, such as a stearyl amine, for the purpose of the improvement in the rate of medicine enclosure, and improvement in the cellular adhesiveness of a synizesis parcel. Although it is known that the liposome of the cation nature containing especially DNA will promote movement into the cell of DNA, i.e., a transfection, it is anxious for what has still higher introductory efficiency, incidence rate, and safety. However, the lipid which can be chosen as a cation-ized lipid is restricted, safety is high and development of the cation-ized lipid for medicine support which discovers high efficiency is desired strongly. Now, as such a cation-ized lipid, although U.S. Pat. No. 4897355, U.S. Pat. No. 5334761, the Japanese patent official report publication number No. 292246 [two to], and the Japanese patent official report publication number No. 108391 [four to] are reported, sufficient effect is not acquired.
[0004]
[Problem(s) to be Solved by the Invention] Therefore, DNA can be introduced into a cell efficiently and safely, and targetting of a medicine can be certainly performed to the affected parts, such as the purposes other than movement into the cell of DNA, for example, a vessel inner-bark injury part, a nephritis, a kidney gun, pneumonia, lung cancer, hepatitis, a liver gun, a pancreatic cancer, and a lymphoma, efficiently and safely, and development of medicine support effective in a DDS treatment is desired strongly.
[0005] Therefore, the purpose of this invention is offering the medicine support which can perform a transfection for a nucleic acid, a polynucleotide, a gene, and its analog efficiently and safely to a cell, and the cation-ized lipid which can form it. Moreover, the purpose of this invention is offering the medicine support which sends a medicine, a peptide, and protein to the target part effectively, the cation-ized lipid which can form it, and medicine support.
[0006]
[Means for Solving the Problem]
(1) The piperidine derivative shown by the following general formula 1.
[0007]
[Formula 3]



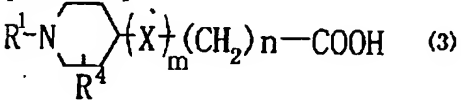
(1)

[0008] R1 is the alkyl group or alkenyl machine of hydrogen and carbon numbers 1-8 among a formula 1. R2 and R3 Or it differs and is the alkyl group or alkenyl machine of hydrogen (however, when both R2 and R3 are hydrogen, it removes), and carbon numbers 1-25. the same -- R4 Hydrogen, the alkyl group of carbon numbers 1-8 or an alkenyl machine, and X are -O- or -S-, m is 0 or 1 and n shows the integer of 0, or 1-10. Moreover, when an asymmetrical carbon exists in a molecule, any of racemic modification and the optically active substance are sufficient as the compound.
[0009] (2) The piperidine derivative shown by the following general formula 2.
[0010]
[Formula 4]



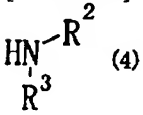
(2)

[0011] Or it differs and is the alkyl group or alkenyl machine of carbon numbers 1-8. the inside of a formula 2, and R1 and R5 are the same -- R2 and R3 Or it differs and is the alkyl group or alkenyl machine of hydrogen (however, when both R2 and R3 are hydrogen, it removes), and carbon numbers 1-25. the same -- R4 Hydrogen, the alkyl group of carbon numbers 1-8 or an alkenyl machine, and X are -O- or -S-, m is 0 or 1 and n shows the integer of 0, or 1-10. Moreover, when an asymmetrical carbon exists in a molecule, any of racemic modification and the optically active substance are sufficient as the compound.
[0012] (3) Medicine support which makes the piperidine derivative of a publication a constituent the above (1) or (2).
(4) Medicine support given in the above (3) which comes to enclose the medicine for diagnosing and/or treating with the aforementioned medicine support.
(5) The above (3) which consists of a minute particle whose path of the aforementioned support is 0.02-250 micrometers, or medicine support given in (4).
(6) The above (3) from which the aforementioned support consists of at least one of a macromolecule, fine aggregate, particle, minute sphere, and nano corpuscle, a liposome, and emulsions, or medicine support given in (5).
[0013] (7) The above (3) whose aforementioned support contains a lipid other than phospholipid or its derivative, and/or phospholipid or its derivative, a stabilizing agent, an antioxidant, and/or other surface ornamentation agents, or medicine support given in (6).
(8) The above (3) whose medicines for above-diagnosing and/or treating are a nucleic acid, a polynucleotide, a gene, and its analog, or medicine support given in (7).
The medicine for above-diagnosing and/or treating (9) An anti-inflammatory agent, an anticancer agent, An enzyme agent, an enzyme inhibitor, an antibiotic, an anti-oxidant, a lipid incorporation inhibitor, a hormone drug, An angiotensin conversion enzyme inhibitor, an angiotensin acceptor antagonist, Proliferation and the migration inhibitor of a smooth muscle fiber, a platelet aggregation inhibitor, the isolation inhibitor of a chemical mediator, The above (3) which is proliferation or the inhibitor, the aldose reductase inhibitor, the mesangial-cell growth inhibition agent, the lipoxygenase inhibitor, the immunosuppresant, the immunostimulator, antivirotic, or radical SUKABEN char of an endothelial cell, or medicine support given in (7).
[0014] (10) The above (3) whose medicines for above-diagnosing and/or treating are a glycosaminoglycan and its derivative, or medicine support given in (7).
(11) The above (3) whose medicines for above-diagnosing and/or treating are oligo and/or polysaccharides, and those derivatives, or medicine support given in (7).
(12) The above (3) whose medicine for above-diagnosing and/or treating is protein or a peptide, or medicine support given in (7).
(13) The above (3) whose medicines for above-diagnosing and/or treating are various in-the-living-body diagnostic drugs, such as X contrast medium, radioisotope indicator nuclear-medicine-diagnosis medicine, and a diagnostic drug for a nuclear-magnetic-resonance diagnosis, or medicine support given in (7).
[0015]
[Embodiments of the Invention] Each compound of this invention is a new compound, and the compound expressed with a general formula (1) can make a carboxylic-acid activator able to react to the carboxylic-acid derivative expressed with the following general formula (3), can be led to the reactant derivative in a carboxyl group, and can be manufactured by subsequently making it react with the amine derivative expressed with the following general formula (4). Moreover, a protective group is desorbed by the well-known method if needed.
[0016]
[Formula 5]



(3)

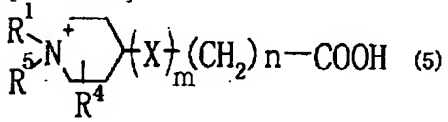
[0017] R1 is hydrogen, the alkyl group of carbon numbers 1-8 or an alkenyl machine, and a suitable protective group (for example, benzyloxycarbonyl machine) among a formula 3, R4 is the alkyl group or alkenyl machine of hydrogen and carbon numbers 1-8, X is -O- or -S-, m is 0 or 1 and n shows the integer of 0, or 1-10.
[0018]
[Formula 6]



(4)

[0019] the inside of a formula 4, and R2 and R3 are the same -- or it differs and the alkyl group or alkenyl machine of

hydrogen (however, when both R2 and R3 are hydrogen, it removes), and carbon numbers 1-25 is shown
[0020] In the reaction of a carboxylic-acid derivative (3) and a carboxylic-acid activator as a carboxylic-acid activator for example, a thionyl chloride, a phosphorus pentachloride, and chloroformate (a KUROROGI acid methyl --) Ethyl chloroformate, an oxalyl chloride, and carbodiimides for example, an N and N'-dicyclohexylcarbodiimide (DCC) -- A 1-ethyl-3-(3-dimethylamino propyl) carbodiimide (WSC), benzotriazol-1-IRU-OKISHI-tris (dimethylamino)-phosphonium Although hexafluorophosphate (BOP) etc. is raised You may use together carbodiimides, an N-hydroxy benzotriazol, 4-dimethylamino pyridine, or a hydroxy succinimid. This reaction is usually performed to the bottom of existence of ether [, such as halogenated hydrocarbons, such as a methylene chloride and chloroform, a tetrahydrofuran (THF), a dioxane, a wood ether, diethylether, and an isopropyl ether,], N.N-dimethylformamide, N, and N-dimethylacetamides or these mixed solvents. Reaction temperature is usually -10 degrees C - 50 degrees C.
[0021] In this reaction, when the acid halide was obtained as a reactant derivative as a carboxylic-acid activator when a thionyl chloride, an oxalyl chloride, or a phosphorus pentachloride was used, the mixed acid anhydride used as the reactant derivative is obtained when chloroformate is used as a carboxylic-acid activator, and carbodiimides are used as a carboxylic-acid activator, activity ester is obtained as a reactant derivative.
[0022] The reaction of the reactant derivative and amine derivative (4) in the carboxyl group of a carboxylic-acid derivative (3) is performed under anhydrous or a water condition among solvents, such as a methylene chloride, a tetrahydrofuran, and an acetone, to the bottom of existence of deoxidizers (a pyridine, a triethylamine, potassium carbonate, a potassium hydrogencarbonate, sodium hydrogencarbonate, etc.), when this reaction derivative is an acid halide. -50 degrees C - 100 degrees C of reaction temperature are -10 degrees C - 30 degrees C preferably. When this reactant derivative is activity ester or a mixed acid anhydride, it can carry out in the solvent used at the reaction with the carboxylic-acid activator of a carboxylic-acid derivative (3), and the same solvent. The reaction time of the reaction temperature in this case is usually 1 - 5 hours at 0-30 degrees C.
[0023] Moreover, the compound shown by the general formula (2) can be manufactured by making a carboxylic-acid derivative (5) and amine guidance (4) react like the compound shown by the general formula (1). Or the compound shown by the general formula (1) can be manufactured alkylation or by alkenyl-izing according to a well-known method.
[0024]
[Formula 7]



(5)

[0025] the inside of a formula 5, and R1 and R5 are the same -- or it differs, and R4 is the alkyl group or alkenyl machine of hydrogen and carbon numbers 1-8, X is -O- or -S-, it is the alkyl group or alkenyl machine of carbon numbers 1-8, and n shows [m is 0 or 1 and] the integer of 0, or 1-10
[0026] the piperidine derivative (1) manufactured and (2) -- the very thing -- isolation extraction can be carried out by well-known separation, the refining means (for example, a chromatography, recrystallization), etc. [thus,]
[0027] The support of this invention has the desirable size 0.02-250 micrometers of whose particle size are especially 0.05-0.4 micrometers. Moreover, although the structure can consider various gestalten and does not need to limit them, at least one or more to a bird clapper is more the most desirable among a macromolecule and the fine aggregate, particle, minute sphere, and nano corpuscle, a liposome, and an emulsion. [which have the potential function which can carry out high concentration enclosure of the medicine especially in the interior]
[0028] In this invention, although it is not necessary to limit to the combination especially if the above-mentioned gestalt can be formed as a constituent of medicine support, when stability is taken into consideration in the safety and in the living body, combination of a lipid other than phospholipid or its derivative, and phospholipid, its derivative or a stabilizing agent, an antioxidant, and other surface ornamentation agents is desirable.
[0029] As phospholipid, nature, such as the phosphatidylcholine (= lecithin), a phospha JIRUGURISE roll, the phosphatidic acid, the phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, a sphingomyelin, and a KARUJI olivine, composite phospholipid, or the thing that hydrogenated these according to the conventional method can be mentioned.
[0030] As a stabilizing agent, saccharides, such as sterols, such as cholesterol with which a membrane fluidity is reduced, or a glycerol, and sucrose, are mentioned. A tocopherol homolog, i.e., vitamin E etc., is mentioned as an antioxidant. Although four isomers, alpha, beta, gamma, and delta, exist, it has set to this invention and a gap can also be used for a tocopherol.
[0031] As other surface ornamentation agents, the derivative of water-soluble polysaccharide, such as a hydrophilic macromolecule, glucuronic acid, a sialic acid, and a dextran, is mentioned. As the aforementioned hydrophilic macromolecule, a polyethylene glycol, a dextran, a pullulan, FIKORU, polyvinyl alcohol, a styrene-maleic-anhydride alternating copolymer, a divinyl ether-maleic-anhydride alternating copolymer, a synthetic polyamino acid, an amylose, an amylopectin, chitosan, a mannan, cyclodextrin, pectin, a carrageenan, etc. are mentioned. The effect of a polyethylene glycol of raising the retentivity in blood is remarkable also in it.
[0032] Moreover, the aforementioned hydrophilic macromolecule can insert a hydrophobic compound part in the film of medicine support (for example, liposome) stably by using the derivative combined with hydrophobic compounds, such as

long-chain fatty alcohol, a sterol, a polyoxypropylene alkyl, or a glycerine fatty acid ester. A hydrophilic macromolecule can be made to exist in a medicine carrier surface by that. A polyethylene-glycol-phosphatidylethanolamine etc. is mentioned as a hydrophilic macromolecule derivative which can be concretely used in this invention.

[0033] In this invention, the pharmacology-active substance, the physiological active substance, or the matter for a diagnosis which can be pharmacologically permitted as a medicine enclosed with medicine support according to the purpose of a diagnosis and/or medical treatment can be used. Although it is [in / the matter / no] fundamentally satisfactory as a property of the medicine to enclose, the matter which is neutrality or anionic electrically can expect the rate of high enclosure from the feature in which the front face of support has positive charge.

[0034] As a kind of medicine for [to enclose] treating, although formation of medicine support is not spoiled, it is not ****(ed) especially limited. Specifically, proliferation promotion or the inhibitor of a nucleic acid, a polynucleotide, a gene and its analog, an anti-inflammatory agent, an anticancer agent, an enzyme agent, an antibiotic, an anti-oxidant, a lipid incorporation inhibitor, a hormone drug, an angiotensin conversion enzyme inhibitor, an angiotensin acceptor antagonist, proliferation and the migration inhibitor of a smooth muscle fiber, a platelet aggregation inhibitor, the isolation inhibitor of a chemical mediator, and an endothelial cell, an aldose reductase inhibitor, a mesangial-cell growth inhibition agent, a lipoxygenase inhibitor, an immunosuppresant, an immunostimulator, an antivirotic

[0035] Moreover, as a kind of medicine for [to enclose] diagnosing, although formation of medicine support is not spoiled, it is not ****(ed) especially limited. Specifically, X contrast medium, radioisotope indicator nuclear-medicine-diagnosis medicine, the diagnostic drug for a nuclear-magnetic-resonance diagnosis, etc. are mentioned.

[0036] Although the medicine support of this invention can be easily obtained by the conventional method, the example is shown below. Other support constituents, such as a piperidine derivative, phospholipid, etc. which are shown by the general formula (1) or (2) in a flask, are mixed by organic solvents, such as chloroform, and a thin film is made to form in a flask wall by carrying out the after [distilling off] vacuum drying of the organic solvent. Next, liposome dispersion liquid are obtained by adding a medicine in the flask concerned and stirring violently. Medicine support can be obtained as dispersion liquid by removing the medicine which was not enclosed by carrying out centrifugal separation of the obtained liposome dispersion liquid, and carrying out the decantation of the supernatant liquid. Moreover, each above-mentioned constituent can be mixed and it can also obtain by carrying out high-pressure **** with a high-pressure **** type emulsifier.

[0037]

[Example] Next, although an example and the example of an examination are given and this invention is explained in more detail, this invention is not limited to these examples and the example of an examination.

(Example 1)

Synthetic 1-(benzyloxycarbonyl)-4-(carboxy methoxy) piperidine 1.17g of an N and N-dioctadecyl-2-(piperidine-4-IRU-OKISHI) acetamide, dioctadecyl amine 2.09g, and benzotriazol-1-IRU-OKISHI-tris (dimethylamino) phosphonium To a hexafluorophosphate 1.95g N.N-dimethylformamide (DMF) (20ml)-methylene-chloride (20ml) solution, it is bottom of ice-cooling, and triethylamine 1.21g. In addition, overnight stirring was carried out at the room temperature. Water was added, ethyl acetate extracted, the organic layer was washed with a dilute acid, water, a dilute alkali, and water in order, and it dried by sulfuric-anhydride MAGUNEUMU, and condensed under reduced pressure. A residue is given to a silica gel chromatography and it is a chloroform elution fraction. N and N-dioctadecyl-2-(1-(benzyloxycarbonyl) piperidine-4-IRU-OKISHI) acetamide 3.14g was obtained (100% of yield, oil).

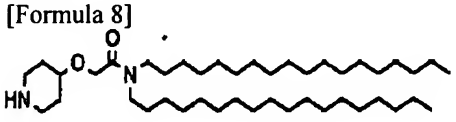
[0038] The bottom of hydrogen atmosphere, and N and N-dioctadecyl -2 -(1-(benzyloxycarbonyl) piperidine-4-IRU-OKISHI)- Overnight stirring of acetamide 1.89g and the ethanol (15ml) suspension of 500mg of 10% palladium carbon was carried out. Vacuum concentration of the filtrate was carried out after filtering a catalyst. The residue was given to the silica gel chromatography and N and N-dioctadecyl-2-(piperidine-4-IRU-OKISHI) acetamide 540mg was obtained from the 5% methanol-chloroform elution fraction (34% of yield, a colorless crystal, 89 to 90 degree C melting point). The instrumental-analysis data of this thing support the structure of the following formula (6).

[0039] 1 H-NMR (CDCl3) delta (ppm):4.15 (2H, s), 3.82-3.76 (1H, m), 3.39-3.08 (8H, m), 2.21-1.99 (4H, m), 1.58-1.46 (4H, m), and 1.34- 1.19 (60H, m) and 0.88 (6H, t, J= 6.80Hz)

FAB-MS(m/z) 664(M+1)

[0040]

[Formula 8]



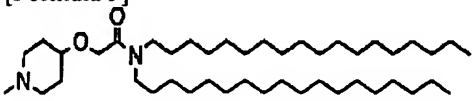
(6)

[0041] (Example 2)

The mixed solution of composition [of an N and N-dioctadecyl-2-(1-methyl piperidine-4-IRU-OKISHI) acetamide] N and N-dioctadecyl-2-(piperidine-4-IRU-OKISHI) acetamide 1.33g, formalin (37%) 179mg, and 1ml of formic acids was stirred at 90 degrees C for 2 hours. Vacuum concentration of the dilute acid was added and carried out, and the dilute alkali was added, it extracted by the methylene chloride, the organic layer was washed with a dilute alkali and water in order, and it dried by sulfuric-anhydride MAGUNEUMU, and condensed under reduced pressure. The residue was given to the silica gel chromatography and N and N-dioctadecyl-2-(1-methyl piperidine-4-IRU-OKISHI) acetamide 1.24g was obtained from the 5% methanol-chloroform elution fraction (92% of yield, a colorless crystal, 50 degrees C of melting points). The

instrumental-analysis data of this thing support the structure of the following formula (7).
[0042] 1 H-NMR (CDCl3) delta (ppm):4.14 (2H, s), 3.52-3.43 (1H, m),
3.28(2H,t,J=8.00Hz),3.23(2H,t,J=8.00Hz),2.80-2.71(2H,m),2.37-2.18(2H,m),2.31(3H,s),2.03-1.93(2H,m),1.77-1.64(2H,m),1.

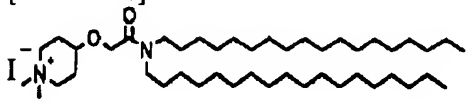
FAB-MS(m/z) 678(M+1)
[0043]
[Formula 9]



(7)

[0044] (Example 3)
779mg of methyl iodides was added to the composition N of an N and N-dioctadecyl-2-(1 and 1-dimethyl piperidine-4-IRU-OKISHI) acetamide, and the N-dioctadecyl-2-(1-methyl piperidine-4-IRU-OKISHI) acetamide 1.24g methylene-chloride (20ml) solution, and overnight reflux stirring was carried out. Reduced pressure distilling off of the reaction solution was carried out. The residue was given to the silica gel chromatography and N and N-dioctadecyl-2-(1 and 1-dimethyl piperidine-4-IRU-OKISHI) acetamide 730mg was obtained from the 5% methanol-chloroform elution fraction (49% of yield, a colorless crystal, the 214 to 217 degree C melting point, recrystallization acetonitrile). The instrumental-analysis data of this thing support the structure of the following formula (8).
[0045] 1 H-NMR (CDCl3) delta (ppm):4.22 (2H, s), 3.93-3.88 (1H, m),
3.83-3.63(2H,m),3.55(3H,s),3.43(3H,s),3.27(2H,t,J=8.0Hz),3.10(2H,t,J=8.0Hz),2.34-2.22(2H,m),2.15-2.03(2H,m),1.60-1.46(

[0046]
[Formula 10]



(8)

[0047] (Example 4) 3microM and cholesterol are dissolved for the N and N-dioctadecyl-2-(piperidine-4-IRU-OKISHI) acetamide compounded in the example 1, and 21microM is completely dissolved for 6microM and a dipalmitoyl phospha CHIJIRU choline (DPPC) in an eggplant type flask with a capacity of 10ml under chloroform of **** and 1ml of **. Reduced pressure distilling off of the chloroform was carried out by the evaporator, and the lipid thin film was formed in the flask wall. Subsequently, liposome (MLV) dispersion liquid were obtained by adding 1ml of 10 mMTris-HCl buffer solutions containing the calcein of 0.5microM to a flask, and carrying out osmosis stirring violently.
[0048] (Example 5) The liposome dispersion liquid which contain N [which was compounded in the example 2] and N-dioctadecyl-2-(1-methyl piperidine-4-IRU-OKISHI) acetamide 3microM, cholesterol 6microM, dipalmitoyl phospha CHIJIRU choline (DPPC) 21microM, and a calcein like an example 4 were obtained.
[0049] (Example 6) The liposome dispersion liquid which contain N [which was compounded in the example 3] and N-dioctadecyl-2-(1-dimethyl piperidine-4-IRU-OKISHI) acetamide 3microM, cholesterol 6microM, dipalmitoyl phospha CHIJIRU choline (DPPC) 21microM, and a calcein like an example 4 were obtained.
[0050] (Example 1 of an examination)
It asked for the rate of enclosure to the liposome of the measurement calcein of the rate of enclosure of a calcein as follows. 40micro of diluted 50 times as many liposome suspension l which was prepared as this is added to 2.0ml 10 mMTris-HCl buffer solution, and fluorescence intensity is measured (excitation wavelength of 490nm, fluorescence wavelength of 530nm). Fluorescence intensity at this time is set to Ft. The calcein which next did 20microl addition of 10mMCoCl(s)2 solution, and was not enclosed with a liposome is made to quench, and the fluorescence of the calcein enclosed with the interior of a liposome is measured. Fluorescence intensity at this time is set to Fin. A liposome is destroyed, it is made to combine with Co2+ and all calceins are made to quench by doing 20microl addition of 20 more%TritonX-100 solution. Fluorescence intensity at this time is set to Fq. The maintenance efficiency of a liposome is calculated by the following formulas.
[0051] Maintenance efficiency (%) =(Fin-Fqxr)/(Ft-Fqx r) x100. [0052] r in a formula is r= (2.0+0.04+0.02+0.02) / 2.0= 1.04 in this experiment in the value which amended the volume change of liposome suspension and the reaction mixture accompanying addition of a medicine. A result is shown in Table 1.
[0053]
[Table 1]

表1

リポソーム分散液	封入率（%）
実施例4で調製したリポソーム分散液	28.4
実施例5で調製したリポソーム分散液	24.3
実施例6で調製したリポソーム分散液	7.7

[0054] (Example 7) Let [the N and N-dioctadecyl-2-(piperidine-4-IRU-OKISHI) acetamide compounded in the example 1] 20microM and a dioleoyl phospha CHIJIRU ethanolamine (DOPE) be 20microM ****, **, and the 1ml chloroform solution A for 10microM and JIRAUROIRU phospha CHIJIRUKORIN (DLPC). 20microl of the chloroform solution A was taken in the eggplant type flask with a capacity of 10ml, and 1 moreml chloroform was added. Reduced pressure distilling off of the chloroform was carried out by the evaporator, and the lipid thin film was formed in the flask wall. 1ml of solution which dissolved plasmid pcDNA/Amp(Invitrogen) 20microg incorporating the gene of beta-galactosodase was added in the flask, and the DNA enclosure liposome was obtained by carrying out osmosis stirring violently.
[0055] (Example 2 of an examination)
Manufacture of a cell, and a transfection cell: Subculture of the Cos-1 cell (ATCC No.CRL-1650) purchased from Dainippon Pharmaceutical Co., Ltd. was carried out using Iscove's modified Dulbecco's medium (IMDM) which contains fetal calf serum (FCS) 10% in 5%CO2 and the 95% O 2 or 37 degrees C incubator.
[0056] Transfection: 10%FCS Cos-1 cell of about 2x104 was added to the 6 hole multi-well plate which added the IMDM culture medium (1ml), and the cell culture was performed. It exchanges for the fresh culture medium which does not contain the about 24-hour cultivation back FCS, and the liposome suspension containing DNA of 0.2microg is added. After 16-hour cultivation, 10%FCS Culture-medium exchange was carried out in the IMDM culture medium, and it cultivated for further 48 hours. The cell was fixed with formaldehyde, 5-bromo-4chloro-3-indolyl-beta-galactopyranoside (X-gal) which is the substrate of beta-galactosidase was added, and the cell which discovered beta-galactosidase was identified. The colored whole cell rate was measured by the image processing. A result is shown in Table 2.
[0057]
[Table 2]
表2

試料	導入細胞比率
実施例7で調製したリポソーム	21.57±0.45
リポフェクチン（市販品）	5.9 ±0.91
ジーントランスファ（市販品）	15.0 ±0.67

リポフェクチン（ライフテクノロジー社製）

ジーントランスファ（和光純薬社製）

[0058] (Acute toxicity) As a result of taking orally and intravenous administration performing an acute toxicity test using an ICR system male mouse (5 weeks old), LD50 of the compound of this invention is all 320mg/kg or more, and high safety was checked compared with effectiveness.
[0059]
[Effect of the Invention] A new piperidine derivative is supplied by this invention as mentioned above. The medicine support which makes the piperidine derivative of this invention a constituent became clear [that the introductory efficiency of the medicine to a cell is high] compared with the conventional medicine support, as shown in the example of an examination. The medicine support of this invention with which the pharmacology-active substance, the physiological active substance, or the matter for a diagnosis which can be permitted pharmacologically was made to enclose from such a feature is very effective to the purpose of treatment and a diagnosis.

[Translation done.]